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SCIENTIFIC DATA REVIEWS
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SEP 17 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: DEET: Review of a dermal absorption study in human volunteers

Caswell No.	346	MRID No.	425785-01
EPA Case No.	819244	PC Code.	080301
DP Barcode:	D187952	Submission No.	S435074

TO: Jane Mitchell / Walter Waldrop, PM Team 71
Special Review and Re-registration Division (H7508C)

FROM: Whang Phang, Ph.D. *Whang Phang 9/14/93*
Pharmacologist
Tox. Branch II/ HED (H7509C)

THROUGH: James Rowe, Ph.D. *James N. Rowe 9/15/93*
Section Head, Section III
and
Marcia van Gemert, Ph.D. *Marcia van Gemert 9/16/93*
Branch Chief
Tox. Branch II/ HED (H7509C)

Toxicology Branch II has been requested to review a DEET dermal absorption study on human volunteers. This study has been reviewed. The DER is attached and the conclusion is the following:

Citation: Selim, S. (1992) Absorption and mass balance of ¹⁴C-DEET after topical administration to healthy volunteers. Unpublished study conducted by Biological Test Center. Study No. P891002. DEC. 3, 1992. Submitted to EPA by DEET Joint Venture/ Chemical Specialties Manufacturers Association. EPA MRID No. 425785-01.

Conclusion: Two groups of healthy human volunteers (6 males/group; ages ranged from 20-29 years) were dermally applied radio-labeled DEET in either 15% solution DEET (ethanol) (12 mg; $\approx 36 \mu\text{Ci}$) or undiluted DEET (15 mg; $\approx 37 \mu\text{Ci}$). The test material was applied on an area of $4 \times 6 \text{ cm}^2$ of the forearm for 8 hrs. The results showed that a small percentage of dermally applied DEET was absorbed. The rate and amount of absorption were greater in the 15% solution DEET-treated individuals than in



the undiluted DEET-treated group. The level of radioactivity in the plasma declined rapidly after cessation of exposure.

The total recovery of the applied radioactivity for 15% solution DEET was 88.74%, and that for undiluted DEET was 94.33%. The radioactivity found in the urine expressed as the percentage of the applied radioactivity was 8.41% and 5.63% for 15% solution DEET and undiluted DEET, respectively. Very little radioactivity was found in the feces (mean <0.1%). The majority of the applied radioactivity remained unabsorbed on the application site (~78% of the applied dose for 15% solution DEET and 83% of the applied dose for undiluted DEET) and was recovered in skin rinsates, swabs, and protective coverings.

Essentially all of the absorbed DEET was metabolized prior to elimination in the urine. A total of 6 metabolites were found, and two of them were major metabolites which were found to be similar to those seen in a rat metabolism study (MRID No. 419944-01). One metabolite resulted from oxidation of the methyl moiety on the aromatic ring of DEET to carboxylic acid while the other one was formed through N-dealkylation of an ethyl group from the amide moiety and the oxidation of the methyl group on the ring (Please see the Discussion section for the structures for these two metabolites and DEET).

The results of the study provide very useful information on the dermal absorption of DEET, and the study is **acceptable**.

Reviewer: Whang Phang, Ph.D.
Tox. Branch II (H7509C)

Whang Phang 9/14/93

Secondary Reviewers: Alberto Protzel, Ph.D.
Tox. Branch II (H7509C)
James Rowe, Ph.D.
Tox. Branch II (H7509C)

Alberto Protzel 9/14/93
James N. Rowe 9/15/93

DATA EVALUATION REPORT

Study Type: Dermal absorption study in human volunteers

Chemical: DEET (N, N-diethyl-m-toluamide)

Caswell No. 346

MRID No. 425785-01

PC Code. 080301

Submission No. S435074

EPA Case No. 819244

DP Barcode: D187952

Sponsor: DEET Joint Venture/Chemical Specialties Manufacturers Association

Testing Facility: The clinical phase of this study was conducted by Pharma Bio-Research Assen, The Netherlands

The analytical portion of the study was performed by Biological Test Center (BTC)
2525 McGaw Ave
P.O. Box 19791
Irvine, CA 92713-9791

The report was also written by Biological Test Center.

Citation: Selim, S. (1992) Absorption and mass balance of ¹⁴C-DEET after topical administration to healthy volunteers. Unpublished study conducted by Biological Test Center. Study No. P891002. Dec. 3, 1992. Submitted to EPA by DEET Joint Venture/Chemical Specialties Manufacturers Association. EPA MRID No. 425785-01.

Conclusion: Two groups of healthy human volunteers (6 males/group; ages ranged from 20-29 years) were dermally applied radiolabeled DEET in either 15% solution DEET (ethanol) (12 mg; $\approx 36 \mu\text{Ci}$) or undiluted DEET (15 mg; $\approx 37 \mu\text{Ci}$). The test material was applied on an area of $4 \times 6 \text{ cm}^2$ of the forearm for 8 hrs. The results showed that a small percentage of dermally applied DEET was absorbed. The rate and amount of absorption were greater in the 15% solution DEET-treated individuals than in the undiluted DEET-treated group. The level of radioactivity in the plasma declined rapidly after cessation of exposure.

The total recovery of the applied radioactivity for 15% solution DEET was 88.74%, and that for undiluted DEET was 94.33%. The radioactivity found in the urine expressed as the

percentage of the applied radioactivity was 8.41% and 5.63% for 15% solution DEET and undiluted DEET, respectively. Very little radioactivity was found in the feces (mean <0.1%). The majority of the applied radioactivity remained unabsorbed on the application site ($\approx 78\%$ of the applied dose for 15% solution DEET and 83% of the applied dose for undiluted DEET) and was recovered in skin rinsates, swabs, and protective coverings.

Essentially all of the absorbed DEET was metabolized prior to elimination in the urine. A total of 6 metabolites were found, and two of them were major metabolites which were found to be similar to those seen in a rat metabolism study (MRID No. 419944-01). One metabolite resulted from oxidation of the methyl moiety on the aromatic ring of DEET to carboxylic acid while the other one was formed through N-dealkylation of an ethyl group from the amide moiety and the oxidation of the methyl group on the ring (Please see the Discussion section for the structures for these two metabolites and DEET).

The results of the study provide very useful information on the dermal absorption of DEET, and the study is **acceptable**.

Methods and Materials

Test Article: Non-radiolabeled DEET (N,N-diethyltoluamide) (technical grade) was 98.8% pure, and it was a clear pale yellow liquid. The test chemical (lot No. A-1-96) was provided to the test laboratory by Morfles Chemical Co.

^{14}C -DEET: The carbon atoms of the aromatic ring of DEET were uniformly labeled as indicated by the asterisks in Figure 1, and the radiolabeled DEET was supplied by Wizard Laboratories, Davis, CA. The radiolabeled DEET had a specific activity of 22 mCi/mmole prior to dilution with unlabeled material and a radiochemical purity of 98.9%, which was verified by the testing laboratory to be 97.87% radiochemically pure.

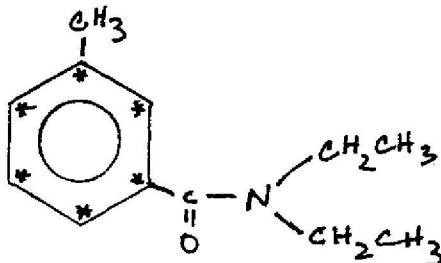


Figure 1. The structure of radiolabeled DEET.

Test subjects : 12 healthy male human volunteers with body weights ranging from 54 to 87 kg and age ranging from 20 to 29 years old were employed in this study.

Study design

1. Preparation of dosing solution: Two dosing solutions were prepared, and the DEET used in these solutions was a combination of ^{14}C -DEET and non-radiolabeled DEET. One solution was a 15% (w/w) DEET solution in ethanol. The other solution was a combination of ^{14}C -DEET and undiluted DEET. The concentration of the radioactivity in the 15% DEET solutions was approximately 36 $\mu\text{Ci}/100\ \mu\text{L}$ or 12 mg DEET/100 μL , and that neat DEET was approximately 37 $\mu\text{Ci}/15\ \mu\text{L}$ or 15 mg DEET/15 μL .
2. Housing of the test subjects: According to the report, on the evening before the initiation of the study, 12 healthy male volunteers reported to the Pharma Bio-Research Clinical Research Center at 7:30 P.M. and were confined at the facility until the completion of the study (6 days). During the study, normal daily exercise with moderate physical activity was allowed. Standard meals were provided at regular hours. Bathing and showering were not allowed until after the last "stripping" on day 3 to prevent any loss of radioactivity from stratum corneum that had not yet been "stripped". The test participants were allowed to leave the research facility at approximately 6:00 P.M. on day 6, provided the amount of the radioactivity in urine had decreased to an acceptable level (3X baseline radioactivity, as derived from the blank 24-hour urine).
3. Test article application and removal after exposure : Each test participant in the 15% (w/w) solution group dermal received 100 μL (12 mg DEET; $\approx 36\ \mu\text{Ci}$ of radioactivity) of prepared test solution, and in the undiluted solution group, each volunteer received 15 μL of the test solution (15 mg DEET; $\approx 37\ \mu\text{Ci}$ of radioactivity). The test solution was applied with a micropipette on to a $4 \times 6\ \text{cm}^2$ skin area of the volar aspect of either the left or right forearm. The test material was spread evenly over the entire application area, and the application was covered with an aluminum dome which was secured with an adhesive bandage. Each aluminum dome contained air holes for circulation. The test material was left on the skin for 8 hours. At the end of the exposure period, the dome was removed, and the application site was cleaned with cotton swabs soaked in isopropyl alcohol. The application site was then rinsed with isopropyl alcohol. The application site cover, cotton swabs, and alcohol rinses were all saved and analyzed for radioactivity. After rinsing, the application area was covered with a dry gauze pad until "stripping". The tape "stripping" was performed at approximately 1, 23, and 45 hours after the end of dosing. The process of tape stripping was done by dividing the $4 \times 6\ \text{cm}^2$ treated area into 6 sections, and each day 2 sections would be stuck repeatedly with 9 mm broad strips of adhesive tape and subsequently pulled off after a few seconds. The number of

strips used for "stripping" each section of the application area was 16. After the last skin "stripping", the area was cleaned. The strips and the cleaning solutions were analyzed for radioactivity.

4. Blood sample collection and analysis: Blood samples (5 ml) were collected into heparinized tubes from each arm at 0 (predose), 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 hours after application of the test article. Each blood sample was centrifuged, and plasma was transferred into a polypropylene tube and stored frozen until analysis.

For analysis, plasma samples were thawed and thoroughly mixed. An aliquot of 0.5 ml was transferred to a liquid scintillation vial. The remainder was saved and stored frozen. All radioactivity measurements were carried using a Beckman LS3801 liquid scintillation spectrometer which was programmed to subtract the background automatically from each sample.

5. Urine sample collection and analysis: The urine samples were collected during the intervals of 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-84, 84-96, 96-108, 108-120, and 120-128 hours after application of the dose. The collected urine samples were weighed and stored frozen. The Methods section did not mention anything about how the background radioactivity was obtained. However, the attached protocol stated that a sample was collected at -24-0 hour (before the initiation of the study), and this sample served as the blank. This reviewer assumed the author of the report overlooked this fact.

For analysis of the radioactivity in the urine, Triplicates of an aliquot of 1.0 ml of urine were transferred into scintillation vials with 20 ml of Insta-Gel and counted with a Beckman scintillation counter.

6. Fecal sample collection and analysis: Samples of feces were collected quantitatively up to 128 hours after application of the dose. Again, the Methods section of the report did not mentioned anything about the sample for the backgroup (blank) measurement. The attached protocol stated that before the initiation of the study, one fecal sample should be collected to serve as a blank .

For radioactivity measurement, samples were homogenized in liquid nitrogen, and approximately 200 mg of feces were weighed directly into the combustion cones to be combusted in a Harvey (Harvey Instrument, Hillsdale, NJ) sample oxidizer. Samples were combusted for 4 minutes. For radioactivity determination, CO₂ from combustion was trapped in a Carbon-14 Cocktail (Harvey Instrument) present in a liquid scintillation counting vial. The radioactivity of each sample was then

measured in a Beckman liquid scintillation spectrometer.

7. High performance liquid chromatography (HPLC) analysis of urine samples: The urine samples of each participant collected during 0-24 hours after application were combined. The radioactivity in the combined urine at the first 24 hours after dosing represented approximately 85% of the radioactivity eliminated by the test subjects. The combined urine was concentrated on Waters C-18 Sep-Paks and eluted with acetonitrile. The acetonitrile eluents were combined under a gentle stream of nitrogen, and for each HPLC analysis, an aliquot of 35 μ L of the concentrate was injected into the HPLC port. Applying similar preparative procedures for concentrating radioactivity, the swab and skin washes were also analyzed.
8. The metabolic profile: The metabolic profile in human urine was determined and compared to that of previously characterized rat urine. An aliquot of 10 μ L of rat urine which was saved from a previous pharmacokinetic study conducted by Biological Test Center (MRID No. 419944-01) was reanalyzed by HPLC. Another aliquot of this rat urine was mixed with a concentrated urine sample from a human volunteer, and the mixture was then injected into the HPLC system. The report stated that identification of the radioactive moieties in human urine was based on similar retention times of radioactivity moieties found in rat urine.
9. Statements of no claims of confidentiality, compliance, and quality assurance were signed and included in the report.

Results

1. Dosing information: For volunteers in the 15% (w/w) solution in ethanol, the mean body weight was 68.6 ± 10.8 kg, and each test individual received 100 μ L of dosing solution containing 12 mg DEET and radioactivity of 35.9 μ Ci. The concentration of DEET on the dermal site (4×6 cm²) was 0.5 mg/cm².

The mean body weight of the volunteers in the undiluted DEET group was 77.6 ± 8.5 kg, and each test subject received 15 μ L of 100% DEET (15 mg) containing 37.0 μ Ci. The dose represented a DEET concentration of 0.62 mg/cm² over the application site (4×6 cm²).

2. Radioactivity in plasma: Blood samples were collected from both contralateral and ipsilateral arms. The radioactivity levels detected in the plasma samples collected from the contralateral arms at various time after dosing were generally below the limit of quantitation (2x background), and they precluded proper evaluation of the results. The means of

radioactivity in the plasma samples collected from the ipsilateral arm of the human volunteers in the two dose solutions at different time intervals are summarized in Table 1, and the values of the individual volunteer are presented in Table 2, A & B.

Table 1*. Mean Plasma Radioactivity Levels at Various Times After Dermal Application

Time (hr)	Mean Total Radioactivity (DPM/500 μ L)	
	15% (w/w) Solution	Undiluted DEET
Predose	0	0
2	165	60
4	279	74
6	269	188
8	384*	158
10	86	61
12	64	21
16	6	3
24	1	0
36	6	0
48	0	0
72	0	0
96	0	0
120	0	0

+: Data excerpted from pages 38 & 49 of the report (MRID No. 425785-01).

*: The magnitude of this value was driven by a single measurement, which was unusually high, for volunteer VL (please see Table 2A).

The values of the mean total plasma radioactivity (presented in Table 1) were plotted by this reviewer in Figure 2. For the 15% solution group, Curve A (broken line) in Figure 1 was plotted using mean values, which included the value of volunteer VL at the 8 hour measurement, whereas Curve B represented the means, which excluded the value of VL at the 8 hour measurement. In general, it was apparent that 15% DEET in ethanol solution was absorbed faster and in substantially larger amounts than the undiluted DEET. The peak level of plasma radioactivity for the 15% solution was 384 dpm at 8 hrs using Curve A; whereas, using Curve B, the peak plasma level was approximately 280 dpm. In the opinion of this reviewer, Curve B seemed to better represent the plasma levels for this dose group. In addition, Curve B roughly followed a similar shape as the curve for the undiluted DEET group whose peak plasma level was 188 dpm at 6 hrs. The pattern of decline of the plasma radioactivity was essentially similar for the two dosing groups. By 8 hrs after removal of the test solution or 16 hrs after dosing, the plasma radioactivity levels

essentially reached 0 (Figure 2). From 16 hrs to the last measurement (120 hrs), the levels remained at the 0 dpm.

3. Elimination of the radioactivity

Urine: The total amount of radioactivity eliminated in urine was 8.33% of the applied dose for the 15% solution group (Table 3A) and 5.61% of the applied dose for the undiluted DEET group (Table 4A). The majority of the radioactivity was eliminated during the interval of 4-12 hours and followed similar patterns for both dose groups (Figure 3). After 48 hours of dosing, very little radioactivity was found in the urine.

Feces: Very little radioactivity was found in the feces of the 15% solution group (<0.10% of the applied dose) and in the undiluted DEET group (0.03% of the applied dose) (Tables 3B and 4B).

4. Radioactivity in strippings, pipets, protective coverings, swabs, and skin rinses: Most of the applied radioactivity was found in skin swabs corresponding to a mean of 50.9% of the applied dose for the 15% solution group and 61.0% of the applied dose for the undiluted DEET group (Tables 5A and 6A, respectively). The covering dome contained a mean of approximately 25% and 21% of the applied dose for the 15% solution DEET group and the undiluted DEET group, respectively. The micropipets contained a mean of approximately 5% and 2% of the applied dose for the 15% solution DEET and the undiluted DEET groups, respectively. The skin rinse and the gauze also contained some radioactivity, but the amount was much less than for the other items mentioned above (Tables 5A and 6A). The total amount of radioactivity recovered in the protective coverings, strippings, pipets, swabs and skin rinses was approximately 80% and 89% of the applied dose for the 15% solution DEET and the undiluted DEET groups, respectively. The data indicated that greater than 80% of applied dose was not absorbed for either dose groups after 8 hrs of exposure, and most of this remained unabsorbed on the application site as indicated by a large percentage of the applied dose being found in the swabs.
5. Total recovery of the applied radioactivity: For the 15% solution group, the total recovery of the applied radioactivity for individual subject ranged from approximately 84% to 91%, and a mean of approximately 89% was found (Table 5B).

In the undiluted DEET group, the total recovery for each volunteer ranged from approximately 87% to 99% of the applied dose, and a mean of 94% of the applied dose was obtained (Table 6B).

6. Analysis of the swab and skin rinses: The swabs and skin rinses of each volunteer in both dose groups were analyzed using HPLC; the results showed that approximately 98% of the radioactivity present in the swabs and skin washes was DEET.
7. HPLC analysis of urinary radioactivity: HPLC analysis did not reveal any intact ^{14}C -DEET in the urine sample of both dose groups of human volunteers. However, 6 discernible peaks, each representing a metabolite, were found in urine samples of both dose groups (Tables 7 & 8 and Figure 4 A & B). The chromatograms showed similar elution patterns for both dose groups. Three metabolites accounted for less than 1% of the applied dose while the others were less than 3% of the applied dose for both dose groups.

In comparing the metabolite profile of DEET observed in humans to that seen in a previously conducted rat metabolism study (Study No. P01836; MRID No. 419944-01), Metabolite 6 seen in humans had similar retention time as Metabolite A of rat urine (Figure 5A), and these two peaks also co-eluted on the mixed urine of rat and human (Figures 4A & 4B and 5B). Metabolite 4 in human urine co-eluted with Metabolite B of rat urine; peak 4, however, was overlapped by another unidentified metabolite (Figure 5B).

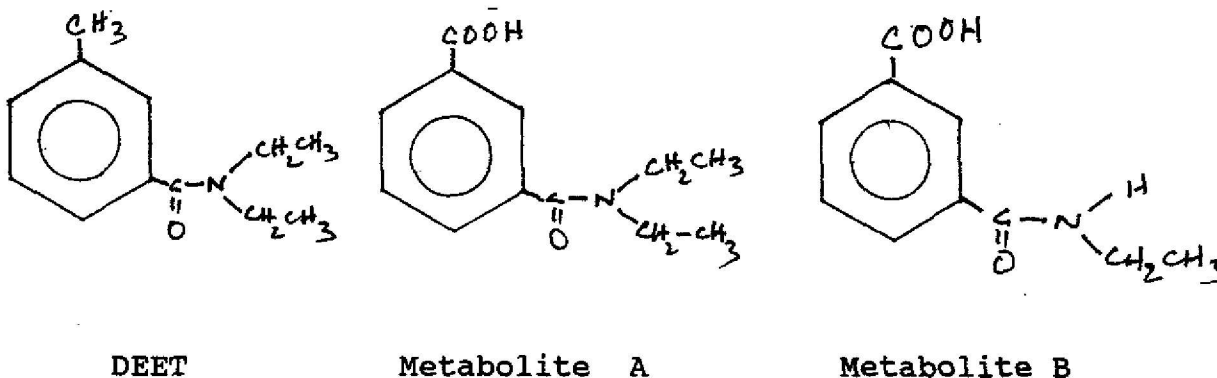
Discussion

Two groups of healthy human volunteers (6 males/group; ages ranged from 20-29 years) were dermally applied radiolabeled DEET in either 15% solution DEET (ethanol) or undiluted DEET. The total amount of DEET applied was 12 mg for the 15% solution ($\approx 36 \mu\text{Ci}$) and 15 mg for the undiluted DEET ($\approx 37 \mu\text{Ci}$). The test material was applied onto an area of $4 \times 6 \text{ cm}^2$ of the forearm for 8 hrs. The results showed that a small percentage of dermally applied DEET was absorbed. The rate and amount of absorption were greater in the 15% DEET in ethanol (w/w) treated group than in the undiluted DEET treated group. After cessation of exposure, the level of radioactivity in the plasma declined rapidly.

The total recovery of the applied radioactivity for 15% solution DEET was 88.74%, and that for undiluted DEET was 94.33%. The major route of elimination of DEET was via urine, and this finding was consistent with the results seen in rat metabolism studies. The percentage of the applied radioactivity found in the urine was 8.41% and 5.63% for 15% solution DEET and undiluted DEET, respectively. Very little radioactivity was found in the feces (mean $< 0.1\%$). Based upon the total recovery of the radioactivity and the radioactivity eliminated in the excreta, a small percentage of the applied dose might have been sequestered in the tissues of DEET.

treated individuals. Mass balance analysis indicated that the majority of the applied radioactivity remained unabsorbed on the application site ($\approx 78\%$ of the applied dose for 15% solution DEET and 83% of the applied dose for undiluted DEET). This analysis gives additional evidence that more DEET was absorbed with 15% solution DEET than with undiluted DEET (by $\approx 5\%$).

The HPLC analysis revealed that all of the absorbed DEET was metabolized prior to elimination in the urine. A total of 6 metabolites were found, and the analysis of the metabolites showed that two major metabolites in the human urine co-eluted with the two known metabolites identified by mass spectroscopy in a rat metabolism study conducted by BTC (MRID No. 419944-01). According to the report, the methyl moiety on the aromatic ring of DEET was oxidized to carboxylic acid to form one of the two major metabolites (Metabolite A) while the other was formed through N-dealkylation of an ethyl group on the amide moiety and the oxidation of the methyl methyl group on the ring (Metabolite B). The structures of DEET and the two major metabolites are presented below:



The author of the report claimed that less than 10% of the dermally applied dose was absorbed by the human volunteers. Based upon the results of this study, this statement might be true for undiluted DEET. However, in the opinion of this reviewer, one could not really make that claim for 15% solution DEET because approximately 11% of the applied dose in the 15% solution DEET group could not be accounted for. It would be true if one were to only interpret the percentage absorbed as that amount being eliminated via urine and feces. In addition, in the rat metabolism study, a small percentage of the applied radioactivity was found in the tissues of the test animals (MRID No. 419944-01).

TABLE 2*

A. TOTAL RADIOACTIVITY IN PLASMA (DPM/500uL) COLLECTED FROM THE IPSILATERAL ARM VEIN FOR VOLUNTEERS ADMINISTERED 14C-DEET AS A 15% SOLUTION IN ETHANOL

POSTDOSE TIME INTERVAL (HRS.)	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	01 D.B.	02 J.D.	03 V.L.	04 M.S.	05 H.V.	06 W.S.	
PREDOSE	0	0	0	0	0	0	0
2	377	168	205	14	209	15	165
4	272	736	160	114	393	0	279
6	206	607	124	148	422	108	269
8	197	590	1071 ^(a)	121	190	134	384 (22)
10	28	122	214	48	54	48	86
12	31	77	128	18	28	101	64
16	3	11	16	3	2	0	6
24	0	0	0	0	7	0	1
36	35	0	0	0	0	0	6
48	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0
120	0	0	0	0	0	0	0

*: MEAN ~~including~~ excluding THE VL value (a)

B. TOTAL RADIOACTIVITY IN PLASMA (DPM/500uL) COLLECTED FROM THE IPSILATERAL ARM VEIN FOR VOLUNTEERS ADMINISTERED UNDILUTED 14C-DEET

POSTDOSE TIME INTERVAL (HRS.)	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	07 G.T.	08 K.Z.	09 S.V.	10 A.E.	11 J.H.	12 H.D.	
PREDOSE	0	0	0	0	0	0	0
2	26	11	45	69	182	27	60
4	58	17	217	40	55	58	74
6	18	74	132	475	339	88	188
8	137	32	64	147	420	147	158
10	30	13	18	127	49	130	61
12	0	9	3	24	33	59	21
16	0	0	0	0	14	6	3
24	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0
120	0	0	0	0	0	0	0

*: DATA EXCERPTED FROM THE REPORT (MRED No. 425785-01)

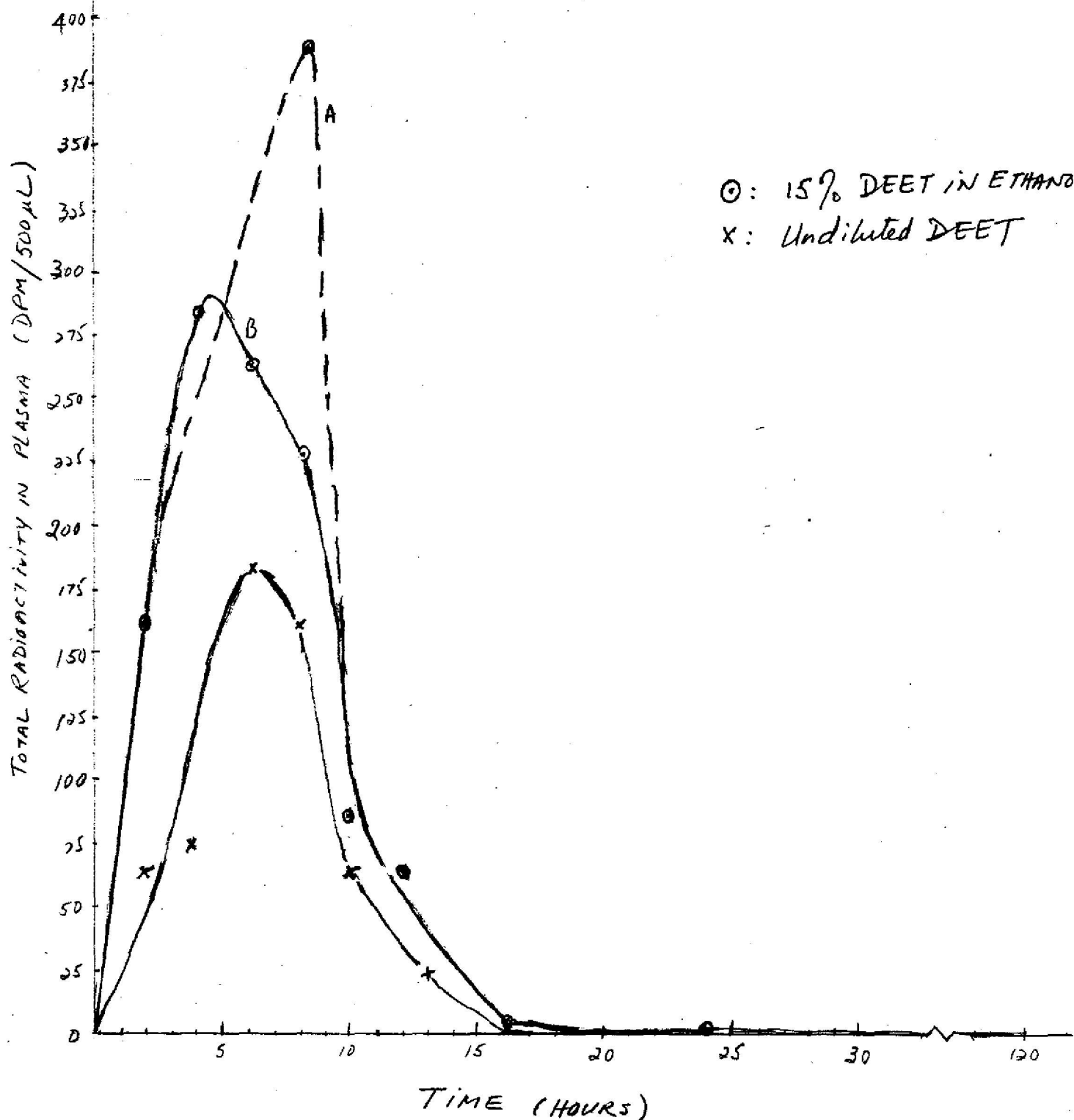


FIGURE 2. MEANS OF THE RADIOACTIVITY IN PLASMA IN BLOOD SAMPLES COLLECTED FROM IPSILATERAL ARM VEIN OF HUMAN VOLUNTEERS ADMINISTERED 15% DEET IN ETHANOL OR UNDILUTED DEET. CURVE A REPRESENTS THE MEAN WHICH INCLUDED THE VALUE OF VOLUNTEER VL AT 8 HRS WHEREAS CURVE B EXCLUDED THAT VALUE IN CALCULATION THE MEAN AT 8 HRS.

TABLE 3⁺

A.

CUMULATIVE PERCENT OF APPLIED DOSE EXCRETED IN THE URINE
FOR VOLUNTEERS ADMINISTERED 14C-DEET AS A 15% SOLUTION IN ETHANOL

POSTDOSE TIME INTERVAL (HRS.)	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	01 D.B.	02 J.D.	03 V.L.	04 M.S.	05 H.V.	06 W.S.	
PREDOSE	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0-4	0.62	0.14	1.32	0.47	0.50	0.10	0.53
4-8	3.52	2.16	6.17	4.83	2.67	1.03	3.40
8-12	6.17	4.62	10.37	8.80	5.10	2.45	6.25
12-24	7.49	5.91	13.23	10.87	6.53	3.64	7.95
24-36	7.67	6.06	13.69	11.15	6.99	3.89	8.24
36-48	7.70	6.09	13.82	11.20	7.06	3.92	8.30
48-60	7.72	6.09	13.87	11.22	7.09	3.93	8.32
60-72	7.72	6.09	13.88	11.22	7.10	3.93	8.32
72-84	7.72	6.09	13.88	11.22	7.11	3.93	8.33
84-96	7.72	6.09	13.88	11.22	7.11	3.93	8.33
96-108	7.72	6.09	13.88	11.22	7.11	3.93	8.33
108-120	7.72	6.09	13.88	11.22	7.11	3.93	8.33
120-128	7.72	6.09	13.88	11.22	7.11	3.93	8.33

B.

CUMULATIVE PERCENT OF APPLIED DOSE EXCRETED IN THE FECES
FOR VOLUNTEERS ADMINISTERED 14C-DEET AS A 15% SOLUTION IN ETHANOL

POSTDOSE TIME INTERVAL (HRS.)	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	01 D.B.	02 J.D.	03 V.L.	04 M.S.	05 H.V.	06 W.S.	
PREDOSE	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DAY 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DAY 2	0.04	0.00	0.00	0.00	0.00	0.07	0.02
DAY 3	0.14	0.01	0.02	0.14	0.03	0.07	0.07
DAY 4	0.14	0.02	0.03	0.15	0.04	0.07	0.08
DAY 5	0.14	0.02	0.03	0.15	0.04	0.07	0.08
DAY 6	0.14	0.02	0.03	0.15	0.04	0.07	0.08

+ : DATA EXCERPTED FROM THE REPORT (MRED No. 425785-01)

TABLE 4[†]

A.

CUMULATIVE PERCENT OF APPLIED DOSE EXCRETED IN THE URINE
FOR VOLUNTEERS ADMINISTERED UNDILUTED 14C-DEET

POSTDOSE TIME INTERVAL (HRS.)	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	07 G.T.	08 K.Z.	09 S.V.	10 A.E.	11 J.H.	12 H.D.	
PREDOSE	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0-4	0.39	0.47	0.30	0.71	0.00	0.07	0.32
4-8	3.08	3.91	1.52	3.09	1.13	0.44	2.20
8-12	5.47	7.30	2.77	5.68	2.16	1.19	4.10
12-24	6.90	9.05	3.43	7.35	2.99	2.32	5.34
24-36	7.16	9.32	3.53	7.52	3.15	2.61	5.55
36-48	7.21	9.37	3.57	7.58	3.18	2.67	5.60
48-60	7.22	9.39	3.57	7.60	3.18	2.68	5.61
60-72	7.22	9.40	3.57	7.61	3.18	2.69	5.61
72-84	7.22	9.40	3.57	7.61	3.18	2.69	5.61
84-96	7.22	9.40	3.57	7.61	3.18	2.69	5.61
96-108	7.22	9.40	3.57	7.61	3.18	2.69	5.61
108-120	7.22	9.40	3.57	7.61	3.18	2.69	5.61
120-128	7.22	9.40	3.57	7.61	3.18	2.69	5.61

B.

CUMULATIVE PERCENT OF APPLIED DOSE EXCRETED IN THE FECES
FOR VOLUNTEERS ADMINISTERED UNDILUTED 14C-DEET

POSTDOSE TIME INTERVAL (HRS.)	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	07 G.T.	08 K.Z.	09 S.V.	10 A.E.	11 J.H.	12 H.D.	
PREDOSE	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DAY 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DAY 2	0.02	0.00	0.00	0.09	0.01	0.00	0.02
DAY 3	0.02	0.01	0.00	0.09	0.01	0.00	0.02
DAY 4	0.02	0.01	0.00	0.09	0.01	0.00	0.02
DAY 5	0.02	0.01	0.00	0.09	0.01	0.00	0.02
DAY 6	0.02	0.01	0.00	0.09	0.01	0.00	0.02

†: DATA EXCERPTED FROM THE REPORT (MRID No. 425785-01).

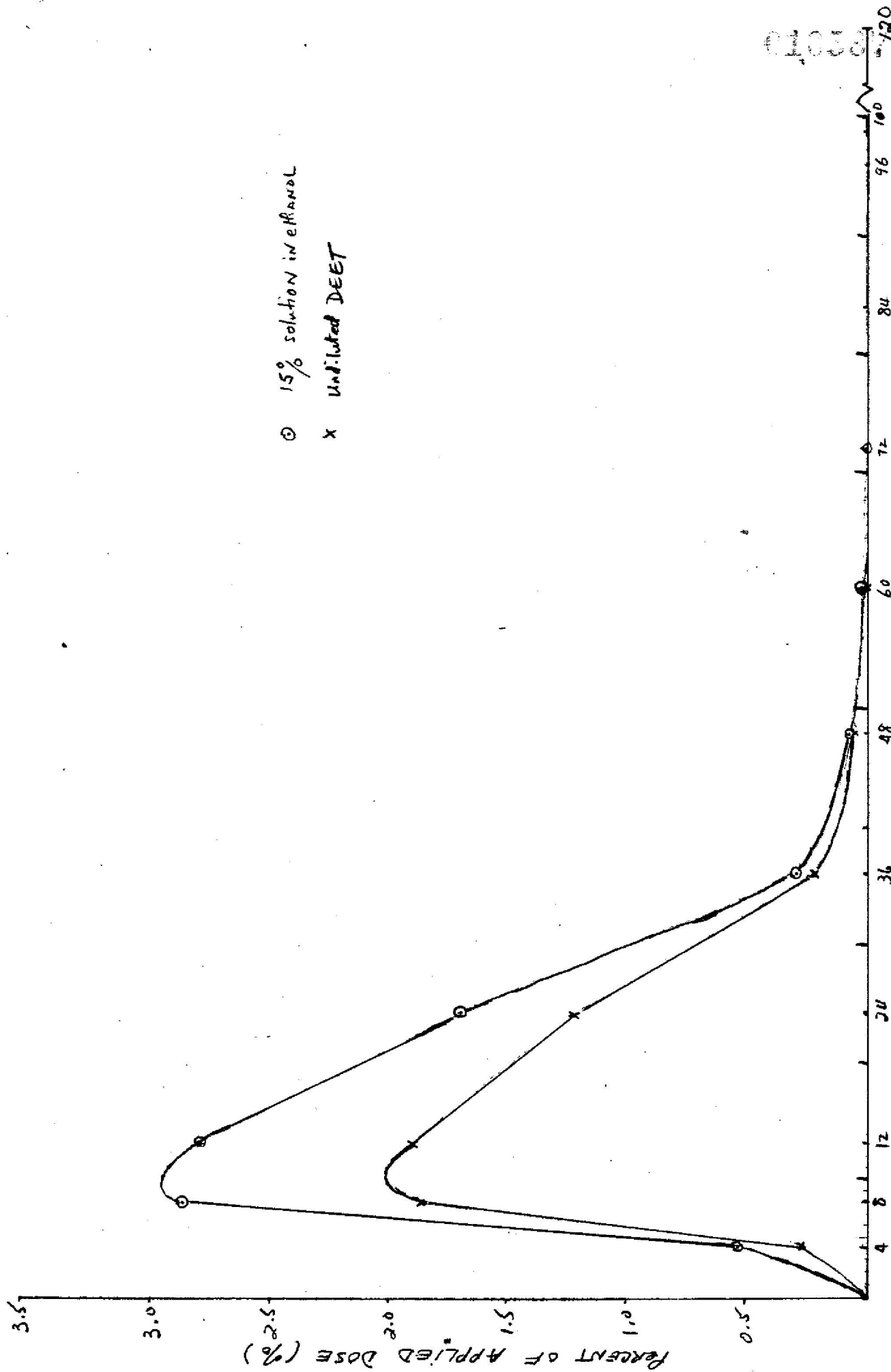


Figure 3. Radioactivity in urine expressed as % of applied dose. The values represented the radioactivity collected over a certain time interval. For plotting purpose the final hour of the interval was used for the X axis.

TABLE 5⁺

A. PERCENT OF APPLIED DOSE RECOVERED FROM APPLICATORS, SWABS, SKIN RINSATES AND PROTECTIVE COVERINGS FOR VOLUNTEERS ADMINISTERED 14C-DEET AS A 15% SOLUTION IN ETHANOL

TYPE OF SAMPLE	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	01 D.B.	02 J.D.	03 V.L.	04 M.S.	05 H.V.	06 W.S.	
PIPETS	0.10	4.41	2.93	2.84	2.10	2.32	2.46
SWABS	62.04	55.45	46.42	19.68	64.16	57.61	50.89
SKIN RINSE	0.37	0.59	2.36	0.64	1.27	1.09	1.05
DOME EXTRACTION #1	16.56	14.15	19.57	42.09	13.65	22.22	21.37
DOME EXTRACTION #2	3.32	3.04	3.32	9.51	2.46	3.37	4.17
GAUZE	0.15	0.09	0.46	0.28	0.50	0.43	0.32
TOTAL:	82.54	77.73	75.06	75.04	84.22	87.04	80.27

B.

TOTAL RECOVERY OF RADIOACTIVITY AS A PERCENT OF APPLIED DOSE FOR VOLUNTEERS ADMINISTERED 14C-DEET AS A 15% SOLUTION IN ETHANOL

SAMPLE TYPE	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	01 D.B.	02 J.D.	03 V.L.	04 M.S.	05 H.V.	06 W.S.	
URINE	7.72	6.09	13.88	11.22	7.11	3.93	8.33
FECES	0.14	0.02	0.03	0.15	0.04	0.07	0.08
TAPE STRIPPING	0.05	0.04	0.06	0.05	0.16	0.07	0.07
OTHER *	82.54	77.73	75.06	75.04	84.22	87.04	80.27
TOTAL:	90.45	83.88	89.03	86.46	91.53	91.11	88.74

* OTHER = APPLICATORS, SWABS, SKIN RINSATES AND PROTECTIVE COVERINGS

+ DATA excerpted from the report (MRED No. 425785-01).

TABLE 6⁺

A. PERCENT OF APPLIED DOSE RECOVERED FROM APPLICATORS, SWABS, SKIN RINSATES AND PROTECTIVE COVERINGS FOR VOLUNTEERS ADMINISTERED UNDILUTED 14C-DEET

TYPE OF SAMPLE	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	07 G.T.	08 K.Z.	09 S.V.	10 A.E.	11 J.H.	12 H.D.	
PIPETS	5.46	4.84	5.24	5.07	5.59	5.78	5.33
SWABS	63.13	54.12	43.12	62.19	70.37	71.87	60.80
SKIN RINSE	1.16	1.51	1.31	0.74	1.00	1.12	1.14
DOME EXTRACTION #1	15.67	14.07	34.79	14.79	14.13	15.38	18.14
DOME EXTRACTION #2	2.49	2.39	5.63	2.65	2.17	2.28	2.94
GAUZE	0.16	0.49	0.20	0.33	0.23	0.25	0.28
TOTAL:	88.07	77.42	90.29	85.77	93.49	96.68	88.62

B.

TOTAL RECOVERY OF RADIOACTIVITY AS A PERCENT OF APPLIED DOSE FOR VOLUNTEERS ADMINISTERED UNDILUTED 14C-DEET

SAMPLE TYPE	VOLUNTEER IDENTIFICATION:						MEAN VALUES
	07 G.T.	08 K.Z.	09 S.V.	10 A.E.	11 J.H.	12 H.D.	
URINE	7.22	9.40	3.57	7.61	3.18	2.69	5.61
FECES	0.02	0.01	0.00	0.09	0.01	0.00	0.02
TAPE STRIPPING	0.07	0.07	0.08	0.10	0.05	0.11	0.08
OTHER *	88.07	77.42	90.29	85.77	93.49	96.68	88.62
TOTAL:	95.38	86.90	93.94	93.57	96.73	99.48	94.33

* OTHER = APPLICATORS, SWABS, SKIN RINSATES AND PROTECTIVE COVERINGS

†: DATA excerpted from the report (MRID No. 425785-01).

TABLE 7 +

DISTRIBUTION OF METABOLITES CALCULATED AS PERCENT OF APPLIED DOSE IN COMPOSITED URINE
FOR VOLUNTEERS ADMINISTERED 14C-DEET AS A 15% SOLUTION IN ETHANOL

VOLUNTEER NUMBER	RADIOACTIVITY EXCRETED IN THE URINE		% OF DOSE											
			ZONE 1		MET. 1		MET. 2		MET. 3		ZONE 2		MET. 4	
			1	2	1	2	1	2	1	2	1	2	1	2
			ZONE	MET.	ZONE	MET.	ZONE	MET.	ZONE	MET.	ZONE	MET.	ZONE	MET.
			1	2	1	2	1	2	1	2	1	2	1	2
01 DB	7.72	0.0	0.8	0.5	1.1	0.2	2.0 ^b	a ^p	0.1	2.8	0.2			
02 JD	6.09	0.0	0.2	0.5	1.0	0.1	0.6	1.1	0.0	2.2	0.4			
03 VL	13.88	0.0	0.0	0.0	1.3	0.3	a ^p	5.8 ^b	0.1	4.0	2.4			
04 NS	11.22	0.4	0.2	0.5	2.6	0.1	0.8	2.3	0.0	3.7	0.6			
05 HV	7.11	0.1	0.5	0.9	1.0	0.0	1.8 ^b	a ^p	0.0	2.2	0.5			
06 WS	3.93	0.2	0.2	0.3	0.6	0.1	0.5	0.5	0.0	1.2	0.3			
MEAN VALUES	8.33	0.1	0.3	0.5	1.3	0.1	1.1	2.4	0.0	2.7	0.7			

^a p = Peak present at the retention time of the metabolite peak but was a shoulder of a larger coeluting peak and could not be accurately integrated.

^b = This value is the total of Metabolite 4 and Metabolite 5.

+ : TABLE excerpted from the report (MREED No. 4248785-01).

TABLE 8[†]

DISTRIBUTION OF METABOLITES CALCULATED AS PERCENT OF APPLIED DOSE IN COMPOSITED URINE
FOR VOLUNTEERS ADMINISTERED UNDILUTED 14C-DEET

VOLUNTEER NUMBER	% OF DOSED RADIOACTIVITY EXCRETED IN THE URINE	% OF DOSE											
		ZONE 1	MET. 1	MET. 2	MET. 3	ZONE 2	MET. 4	MET. 5	ZONE 3	MET. 6	ZONE 4		
07 GT	7.22	0.0	0.5	0.5	1.0	0.0	1.0	0.8	0.0	3.1	0.4		
08 KZ	9.40	0.0	0.4	0.8	1.3	0.2	1.0	1.4	0.0	3.8	0.6		
09 SV	3.57	0.0	0.0	0.1	0.6	0.0	^a P	1.1 ^b	0.2	1.1	0.3		
10 AE	7.61	0.4	0.2	0.2	2.0	0.0	^a P	1.8 ^b	0.1	1.8	0.9		
11 JH	3.18	0.0	0.1	0.2	0.7	0.1	0.4	0.5	0.0	1.0	0.1		
12 HD	2.69	0.1	0.1	0.1	0.3	0.0	0.2	0.4	0.1	1.0	0.3		
MEAN VALUES	5.61	0.1	0.2	0.3	1.0	0.1	0.7	1.0	0.1	2.0	0.4		

^aP = Peak present at the retention time of the metabolite peak but was a shoulder of a larger coeluting peak and could not be accurately integrated.

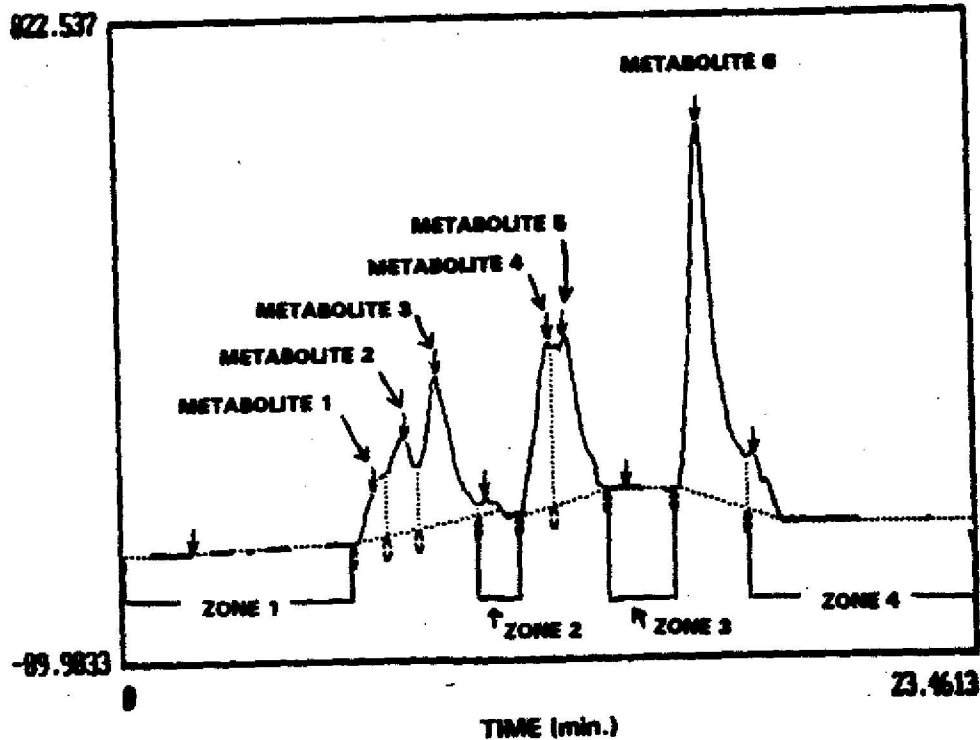
^b = This value is the total of Metabolite 4 and Metabolite 5.

[†]: Table excerpted from the report (MRED No. 425785-01).

Figure 4⁺

010537

A Example of an HPLC Profile and Designation of Metabolites in Urine of Volunteer 02 JD who was Administered ¹⁴C DEET as a 15% Solution in Ethanol



B. Example of an HPLC Profile and Designation of Metabolites in Urine of Volunteer 08 KZ who was Administered Undiluted ¹⁴C DEET

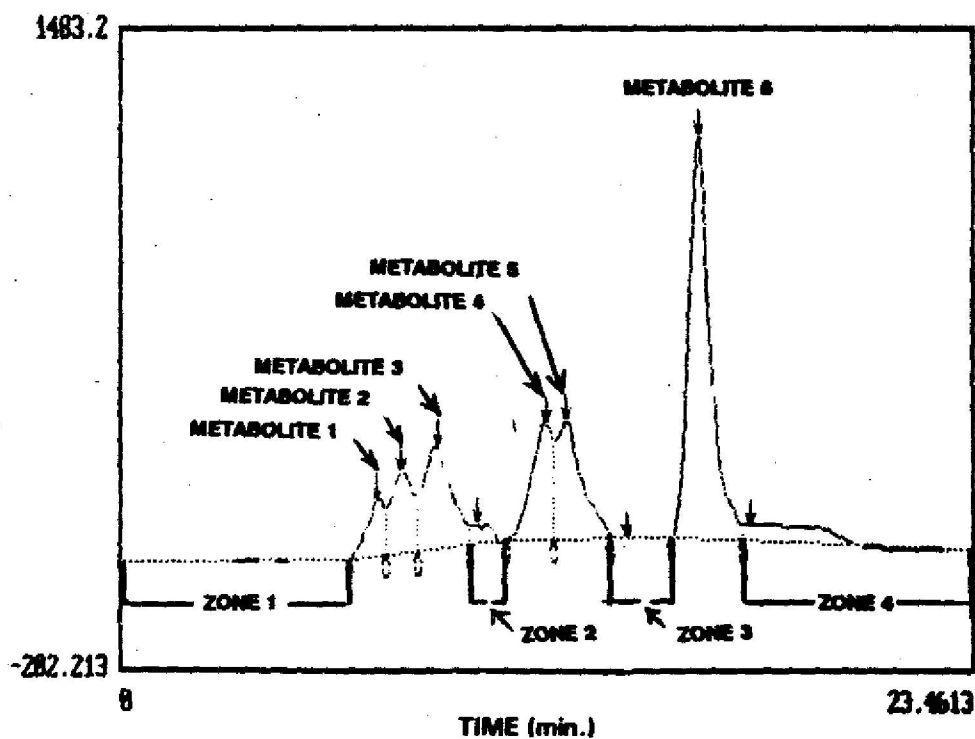
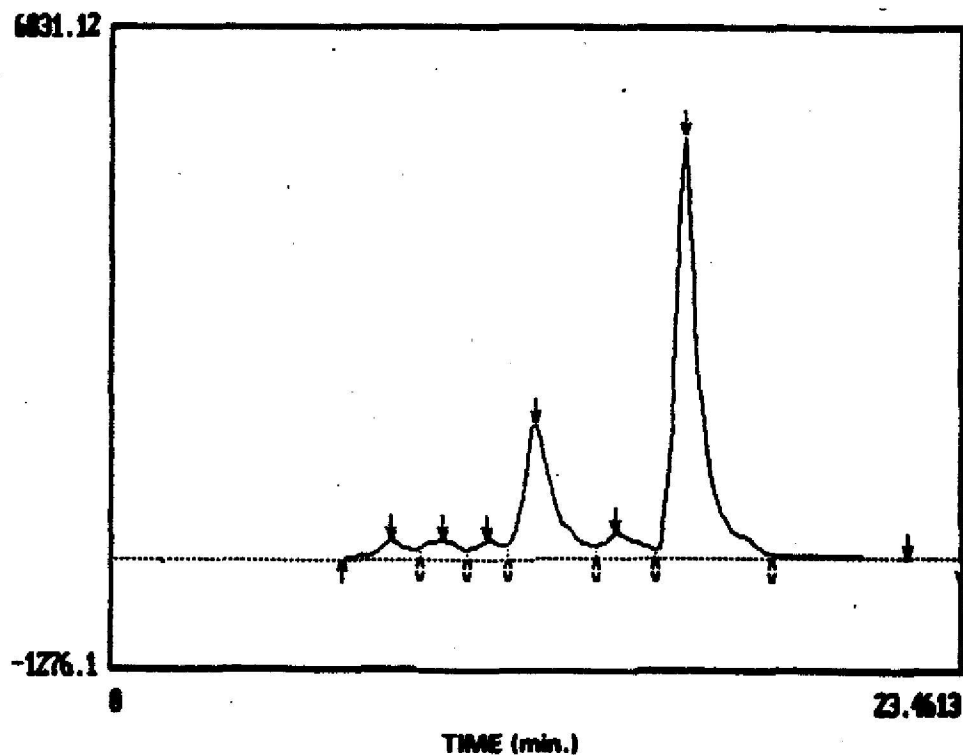
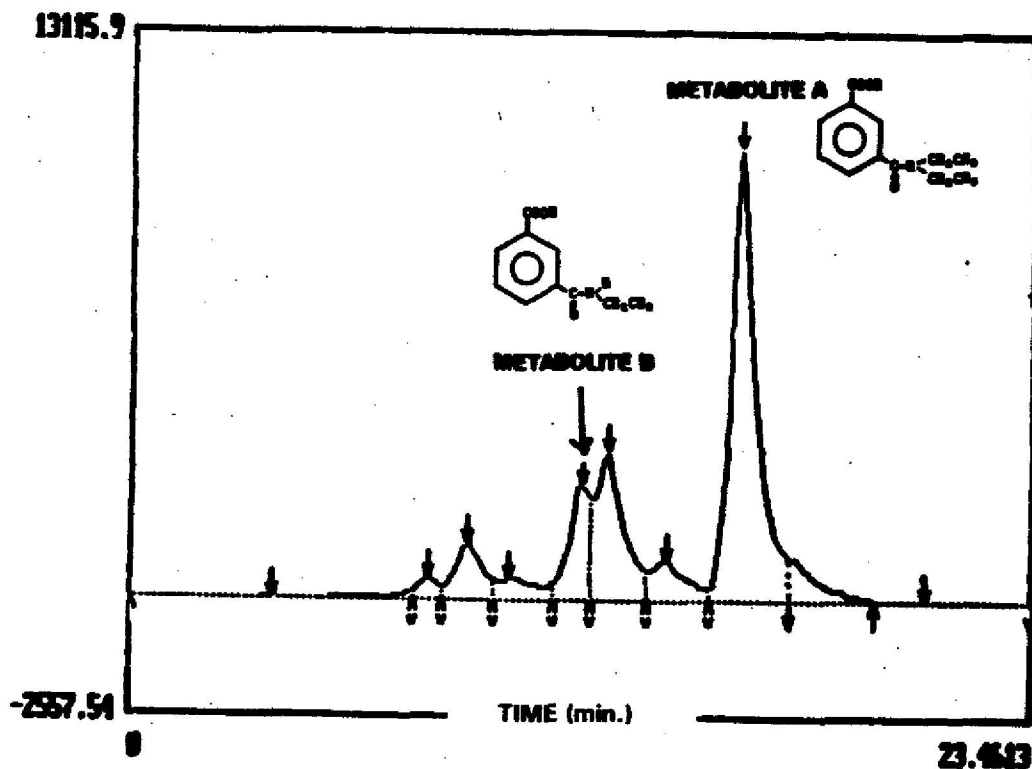


Figure 5[†]

A. HPLC Profile of Composited Rat Urine from BTC Study No. P01836



B. HPLC Analysis of Rat Urine Mixed with Volunteer 03 VL Urine





13544

009391

Chemical: N,N-Diethyl-meta-toluamide and other iso

PC Code: 080301
HED File Code 13000 Tox Reviews
Memo Date: 09/17/93
File ID: TX010587
Accession Number: 412-02-0004

HED Records Reference Center
10/01/2001

